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INTRODUCTION AND OVERVIEW

Assessing children's exposure to hazardous environmental chemicals: an overview of selected research challenges and complexities

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There is renewed interest in the United States regarding characterization of children's exposures to hazardous environmental chemicals. Many studies are currently underway that use novel and innovative approaches to assess childhood exposures to a variety of toxic chemicals, including both persistent and nonpersistent compounds. This article reviews some of the critical challenges that can impede scientifically rigorous studies designed to measure children's environmental exposures. The discussion briefly examines three topical areas: administrative issues (IRB approval, participant incentives, community involvement, and communication of results to research participants and stakeholders); data-collection issues (identifying and recruiting children/families, measuring actual exposures/doses); and issues related to chemical analysis of biological samples (examples of chemicals and chemical classes that can be measured in human tissue and excreta, effects of a child's age on the type and amount of biological samples available for analysis). These research complexities are discussed in the context of developing more effective and efficient exposure assessment methods. *Journal of Exposure Analysis and Environmental Epidemiology* (2000) **10,** 611–629.

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Introduction

It is a well established precept in the field of environmental health that children are potentially more vulnerable than adults because they are both more exposed to many hazardous chemicals and more susceptible to related health effects (Guzelian et al., 1992; Bearer, 1995; Aprea et al., 2000). Scientists and regulators have known for a long time that children differ substantially from adults in terms of exposures (different sources, pathways, and routes of exposure, greater intake of air, soil, dust, food, and beverages per unit body weight and surface area), physiological factors (greater circulatory flow rates, higher cell proliferation rates in many organs), pharmacokinetics (different dermal, intestinal, and respiratory absorption rates, different metabolic efficiencies, developmental changes in membrane permeability and binding and storage of xenobiotics), and pharmacodynamics (immature host defenses) (EHP, 1995,1998a,b,1999; Dearry and Collman, 1999; Rylander and Etzel, 1999). It is only relatively recently, however, that decision makers have tried to formulate and implement public policies aimed at systematically preventing or reducing environmental health risks for children (NRC, 1993; Landrigan and Carlson, 1995; Rogan, 1995; Wargo, 1998; Kaiser, 1999).

Virtually everyone agrees that sound science is the foundation for informed, reasonable, and credible decisions about safeguarding children's environmental health. Policymakers are nevertheless faced with a chronic problem — the continuing shortage of appropriate and adequate scientific information necessary to estimate children's environmental health risks with an acceptable degree of certainty (Mukerjee, 1998; Buffler, 1999; EPA, 1999a; Adgate and Sexton, 2000; EHP, 2000; Hubal et al., 2000a,b; O'Fallon et al., 2000; Schneider and Freeman, 2000). The solution is to develop improved knowledge and better understanding of: relevant exposures, including magnitude, duration, frequency, and timing, as well as the contributions of important sources and pathways; and related dose–response relationships for individual environmental chemicals and real-world mixtures.

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This article examines selected challenges and complexities that confront researchers and risk assessors as they endeavor to better characterize children's exposures to hazardous environmental chemicals. In doing so, it summarizes and integrates important themes that emerge from the articles in this special issue on assessment of children's environmental exposures. The discussion begins with a brief overview of three core issues that are an intrinsic part of childhood exposure assessment — consideration of biological, physical, and social determinants of a child's environmental health; cognizance of the effects of a child's developmental status on exposure-related variables; and decisions about study objectives and exposure assessment methods. The discussion then shifts to an examination of three categories of factors that commonly complicate efforts to assess children's actual exposures — administrative issues, data-collection issues, and issues related to chemical analysis of biological samples. The goal is to stimulate dialogue about innovative approaches and creative solutions for overcoming obstacles, thereby fostering better, more cost-effective ways for assessing children's environmental exposures.

Overview of core issues

Assessment of children's exposures necessarily involves three intrinsic factors: the influence of biological, physical, and social environments on the child's environmental health; variations in exposure-related attributes by developmental stage; and certain crucial realities of the exposure assessment process itself. These topics constitute a set of core issues that affect, either implicitly or explicitly, the nature and scope of exposure assessments aimed at characterizing children's contact with hazardous environmental chemicals.

Determinants of Children's Environmental Health

A child's environmental health and well being can be thought of as occurring at the intersection of three causal domains; his or her physical, biological, and social environments (Bearer, 1995). Individually and in combination these domains are the primary determinants of (1) exposure — contact with a hazardous environmental chemical(s) for a specified period of time, (2) susceptibility — personal vulnerability to the adverse health

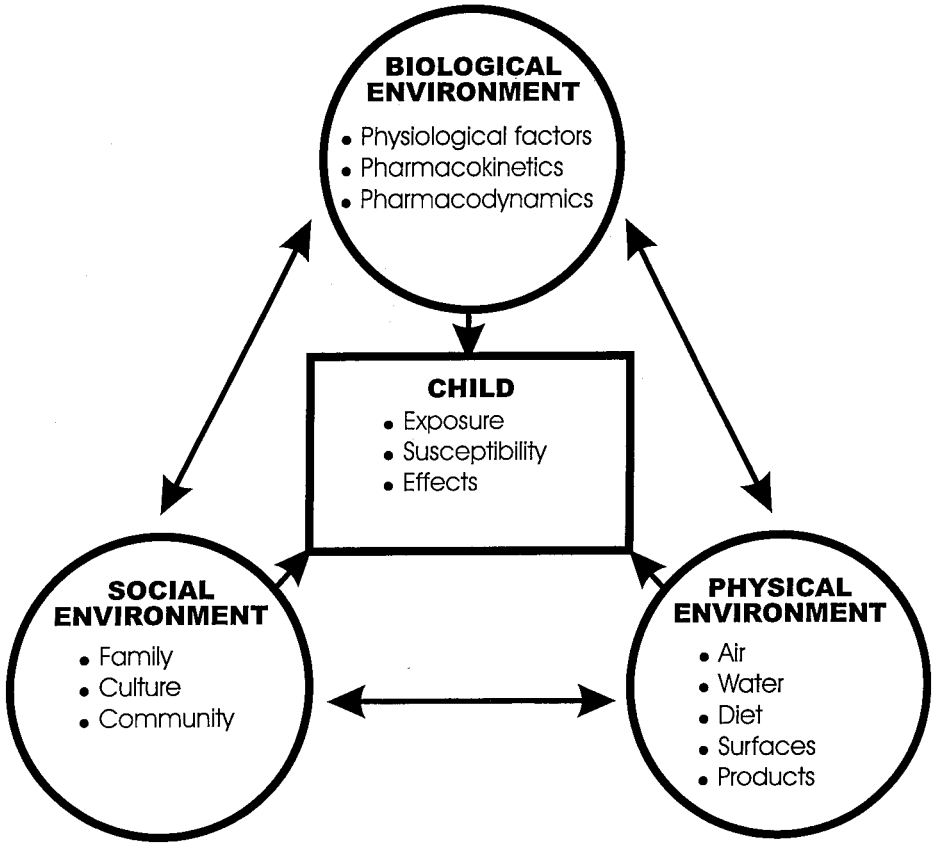

Figure 1. Schematic representation of three causal domains that affect children's environmental health (adapted from Bearer, 1995).

outcomes related to exposures, and (3) effects — health consequences that are caused or exacerbated by exposures (see Figure 1).

The physical environment refers to environmental media and associated hazardous agents that children may come into contact with as a result of normal daily activities, behaviors, and interactions. It encompasses the air they breathe, the food and beverages they consume, the surfaces they contact, and the products they use or encounter. The biological environment refers to relevant aspects of each child's own biological functions and processes. It includes the child's physiological makeup (e.g., height and weight, respiration rate, cell proliferation rate), as well as important pharmacokinetic (e.g., bioavailability, absorption, deposition, metabolism, elimination), and pharmacodynamic (e.g., compensatory, damage, and repair mechanisms) factors. The child's family, culture, and community comprise his or her social environment. The family milieu, which has a direct effect on the child's behaviors and lifestyle, is embedded within and influenced by cultural and community norms that help shape attitudes, beliefs, and values. Prevailing societal standards and world views affect how the child's family, culture, and community are integrated within the social order, and influence public policy decisions about laws and regulations to protect children's environmental health.

Researchers, risk assessors, and risk managers must be cognizant of all three causal domains and take account of important interactions as they strive to identify and address unacceptably high childhood exposures. This kind of holistic approach is necessary if we are to make real progress toward protecting and improving children's environmental health.

Developmental Stages

Although it is common to speak of children as a homogeneous group, there are in fact important exposure-related differences associated with a child's age. For example, an infant's activities, which typically include crawling, climbing, and rolling, increase contact with contaminated surfaces (e.g., floor, ground) and thereby increase the potential for dermal absorption. Young toddlers often put their hands and other objects in their mouth, resulting in nondietary ingestion from contaminated surfaces. Elementary-school-aged children spend a significant portion of their time at school and playing outdoors, where they can come into contact with contaminated air, water, and surfaces. A summary of developmental stages, their duration, and examples of important developmental milestones and exposure-related activities and behaviors is provided in Table 1. It is vitally important to consider age-related exposure differences when designing and implementing studies to characterize children' s exposure, when estimating exposure and dose for risk-assessment purposes, and when deciding how best to manage associated health risks.

Table 1. Summary of developmental stages, relevant time periods, developmental milestones, and exposure-related activities and behaviors (adapted from Adgate and Sexton, 2000).

Developmental stage	Time period	Examples of developmental milestones	Examples of exposure-related activities and behaviors
Embryonic	8 days to 8 weeks of pregnancy	human organogenesis at approximately days 20 to 60 of gestation	mother's exposure to nonpersistent pesticides or release of stored persistent pesticides from adipose tissue
Fetal	8 weeks of pregnancy to birth	control of autonomic nervous system at approximately 24 weeks	trans-placental transfer of mother's exposure to alcohol, drugs, and tobacco
Infancy	birth to 12 months	rolling over at 2 to 3 months, sitting at 3 months, standing with support at 6 months, walking begins at 10 to 17 months, weight triples and height increases approximately 20 cm during first year	transition to solid food begins at 6 to 9 months, diets typically less diverse than adults, mouthing nonfood objects begins as early as 4 months and continues till at least 2 years, breastfeeding is an important exposure pathway for some children
Childhood	1 to 12 years		
Young toddlers	1 to 2 years	language/self feeding at about 1 year	hand-to-mouth behavior common for 1 to 3 year olds, periodic consumption of nonfood objects by 1 to 3 year olds, increasing time spent outside the home — playing, in daycare, at school, and in transit
Older toddlers	2 to 3 years	bladder/bowel control at about 2 years	
Pre-schoolers	3 to 5 years	mastery of motor skills by about 5 years	
School-aged	5 to 12 years	specific synapse formation in the brain	
Adolescence	12 to 18 years	maturation of organ systems to adult size and weight	diverse diets and activity patterns, potential for occupational exposures

Exposure Assessment Realities

There are two critical features of any exposure assessment, whether for adults or children, which shape both the process and the outcome: the assessor's objective(s) and the type of assessment selected to achieve the objective(s).

An assessment of children's exposure is usually undertaken to achieve one or more of four interrelated objectives: (1) to evaluate the current status, historical trends, or possible future directions of exposure in human populations; (2) to investigate causal links between exposure and effect as part of an epidemiologic study; (3) to estimate exposure quantitatively in conjunction with health risk assessment; or (4) to aid in management decisions about which exposures/risks are most serious and what to do about them (see Figure 2). The specific objective(s) of an assessment, in combination with other factors such as budgetary constraints and feasibility issues, determines which approaches, designs, methods, and techniques are appropriate for characterizing exposure in a particular instance.

In practice, both qualitative and quantitative approaches can be used to achieve the stated objectives and describe children's environmental exposure and related dose. Typically, however, quantitative assessments predominate and fall into three broad categories: exposure measurements, reconstructive analysis, and scenario-based approaches (Sexton et al., 1995). Actual exposure measurements are of two types, direct and indirect. Direct (point-of-contact) measurements document exposures as they occur by measuring the pollutant concentration at the point of contact between the child and the environmental (or carrier) medium. Examples include passive dosimeters to measure airborne concentrations near the breathing zone, duplicate diet samples to measure dietary concentrations, or hand-wash samples to measure dermal concentrations. Indirect measurements typically involve a combination of environmental sampling in relevant microenvironments through which children move during their normal routine (e.g., indoors at home, daycare, or school) and data on the amount of time they spend in these microenvironments or engaging in exposure-related activities (e.g., playing on the floor, hand-to-mouth activity). It is worth noting that the use of biological markers to estimate exposure, which we describe below as a separate approach (as is conventional), can be thought of as another form of indirect measurement. The strength of direct and indirect exposure measurements is that they provide solid evidence of the magnitude, duration, frequency, and timing of children's actual exposures. The weaknesses are that costs are relatively high, monitoring can be time-consuming and burdensome for participants, and suitable monitoring devices are not available for all environmental agents, pathways, and settings of interest.

Reconstructive analysis uses measurement of dose (e.g., body burden, elimination levels), in conjunction with information or assumptions about rates of intake and

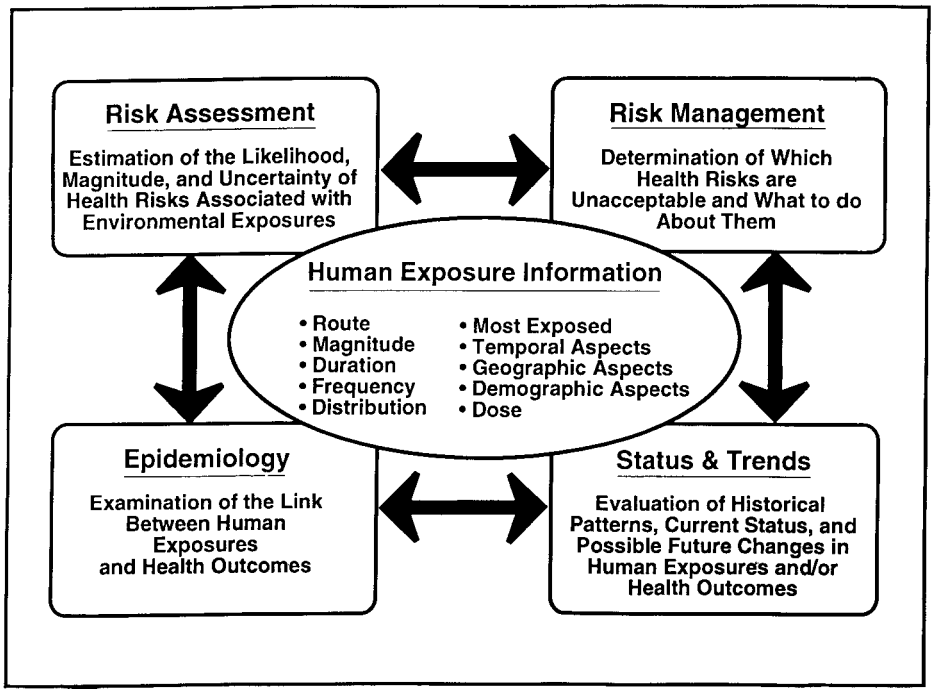

Figure 2. Four major uses of human exposure information and their interrelationships (adapted from Sexton et al., 1992).

uptake, to derive (or reconstruct) estimates of past exposures. Use of this approach requires (1) valid measures of exposure biomarkers in accessible human tissues (e.g., blood, hair) or excreta (e.g., urine, feces) to characterize internal dose, and (2) adequate information to estimate rates of intake, uptake, and metabolism so that exposure can be reconstructed realistically. In general, the strengths and limitations of biomarkers are well known (NRC, 1989a,b,1992; Hulka et al., 1990; Lubin and Lewis, 1995; Bearer, 1998). The values of this approach are its capacity to demonstrate unequivocally that exposure and uptake have occurred and to integrate dose over all exposure routes and pathways. The primary drawbacks are that it can be intrusive and resource intensive and that it does not usually provide information on sources, pathways, or routes of exposure (an exception occurs when a child is exposed to agents that are specific to a particular source, pathway or route, such as environmental tobacco smoke). This approach is also constrained by the lack of unique biological markers for assessing exposures to some chemicals, breakdown of the parent compound into other products that may not be unique to the chemical(s) of concern, endogenous production of the chemical(s) of concern, and lack of physiologically based pharmacokinetic models for many chemicals of interest.

When measurements of exposure and dose are unavailable or not feasible, exposure assessors in federal, state, and local regulatory agencies often rely on scenario-based approaches to estimate exposures. A scenario-based assessment involves the use of available information (e.g., data, databases, models) in combination with assumptions, inferences, and professional judgment to construct a plausible exposure scenario that describes quantitatively how contact occurs between humans and hazardous environmental agents. A typical scenario-based assessment estimates children's exposure by merging information on two key variables: (1) concentrations of an environmental chemical in the carrier medium of interest, estimated by using available monitoring data or making assumptions about source–pathway–exposure interactions; and (2) children's contact time with the carrier medium, estimated by using existing demographic, geographic, and time–activity data, or by making reasonable assumptions about activity patterns, lifestyle characteristics, residential proximity to sources, and other relevant variables (Akland et al., 2000; Hubal et al., 2000a). Related doses are estimated by using knowledge and assumptions about important pharmacokinetic processes.

An example of scenario-based evaluation is the use of pathway–exposure factor (PEF) methods, which combine measurements in important environmental media (e.g., air, water, food, dust, soil) to estimate exposures, with off-the-shelf exposure factors (e.g., volume of air breathed or water consumed per day, body weight and surface area) from U.S. Environmental Protection Agency documents, such as the *Exposure Factors Handbook* (EPA, 1997) and the report on *Sociodemographic Data Used for Identifying Potentially Highly Exposed Populations* (EPA, 1999b) to estimate intake and uptake. The primary advantage of scenario-based approaches is that they allow for estimates of both current and future exposures even when data are limited or lacking, which is usually the case. The primary disadvantage is the uncertainty introduced by the need to make assumptions and inferences because of inadequate or inappropriate information.

These three assessment types are complementary rather than competing methods for characterizing environmental exposures. Selection of an appropriate approach will depend on situation-specific variables, such as the objective(s) of the project, the age range of the children, available resources, and practical realities and technical feasibility of exposure/dose monitoring for the population of interest.

Challenges of assessing children's exposure

With these core issues in mind, we now briefly review major challenges and complexities that commonly confront researchers as they strive to better characterize children's exposure to hazardous environmental chemicals. The focus is on highlighting important issues and problems associated with measurement of children's actual exposures and exposure-related variables. The discussion is divided into three sections: administrative issues, data-collection issues, and chemical-analysis issues.

Administrative Issues

We use the term "administrative issues" to mean those nontechnical but critical aspects of assessing children's exposure that cut across data-collection and chemical-analysis activities. The four issues — (1) securing approval for the study from an Institutional Review Board (IRB), (2) providing suitable incentives for children and families to participate in the study, (3) encouraging meaningful involvement in the project by neighborhoods and communities, and (4) communicating results effectively to participants and other interested parties — are crucial but often under-appreciated components of most childhood exposure studies. Although not well described in the scientific literature, the successful resolution of these and related administrative issues is a prerequisite for effective and efficient studies of children's environmental exposure. Typically, researchers must make a substantial up-front investment of time and effort to achieve satisfactory and timely solutions to these types of administrative challenges.

Our intent here is not to provide a comprehensive list but rather to highlight several key administrative issues that are

commonly encountered in the course of studies to characterize children's exposures. Because each study is different (e.g., specific goals, aims, and approaches) and occurs within the context of unique situations, settings, and circumstances (e.g., particular age-related and socioeconomic characteristics of the children/families), we make no attempt to provide standardized answers to these project-specific administrative challenges. Instead, the reader is referred to several articles in this special issue that describe how individual research teams dealt with these challenges (see, for example, Adgate et al., 2000; O'Rourke et al., 2000; Jordan et al., 2000; and Sexton et al., 2000).

Obtaining Approval from an Institutional Review Board All research involving human subjects comes under the purview of Department of Health and Human Services (DHHS) Regulations for Protection of Human Subjects (45 CFR 46), which require, among other things, that researchers obtain approval from a sanctioned IRB prior to implementing research. Although the DHHS regulations address protections for children participating in research, the National Institutes of Health (NIH) recently established a "policy and guidelines on the inclusion of children as participants in research involving human subjects" (released March 6, 1999). These guidelines are part of an attempt by NIH to "increase the participation of children in research so that adequate data will be developed to support the treatment modalities for disorders and conditions that affect adults and may also affect children."

A major role of IRBs is to ensure that children are not exploited or harmed when they are the subjects of research. Consequently, IRBs have special review requirements under both the DHHS regulations and the NIH guidelines to protect the well being of participating children (a child is defined by NIH to be any person under the age of 21). It is the responsibility of the IRB to ensure that research satisfies the conditions set forth in the regulations as they relate to risk, benefit, parental/guardian consent, child assent, and involvement of children who are a ward of the state or other institution. The IRBs often raise questions about the relative benefits and risks of the proposed research. They typically want assurances that intensive exposure and health measurements are not unduly burdensome and do not intrude unnecessarily into homes and schools, potentially disrupting lives and educational pursuits.

The DHHS regulations require a child's parent or guardian to give "informed consent" for the child to participate in the research project by reading and signing a consent form, which explains in simple understandable terms the risks and benefits of the study, what is being asked of the participants, and any rewards (incentives, inducements, reimbursements, payments, compensations) offered to participate. The regulations also require that a child give his or her "informed assent" (if practicable, based on age and development) to participate in the study by reading (or being read) an assent form, which explains the research project in language commensurate with the child's age and capabilities. It is important that consent and assent forms be simple, direct, and easy to understand.

It is also necessary to obtain the child's verbal assent (if practicable, based on age and development) each time he or she performs a research-related task, such as providing a blood or urine sample, wearing a personal monitor, performing a lung-function test, or keeping an activity diary. The child must be excused from the activity if he or she refuses outright, demurs, looks frightened, or appears agitated. To meet this requirement, field technicians must describe what will happen prior to beginning all research-related activities and must ask the child whether he or she wants to continue with a test (e.g., spirometry) or sample collection (e.g., blood, urine). If the child expresses any reservation, he or she should be excused from participating in that task.

Despite the fact that all IRBs are formed for the same reasons and constituted under the same general guidelines, each has its own idiosyncrasies. Thus, it is important for investigators to become familiar with the preferences and precedents of their particular IRB, using this knowledge to foster a close working relationship that is both collaborative and constructive. For studies that require approval from multiple IRBs, it is essential to coordinate submissions so as to avoid unnecessary delay.

Providing Incentives for Participation One area that is notorious for the diversity of IRB opinions is the subject of incentives for children and families who agree to participate in research projects. Certain IRBs prefer (or insist on) the use (or avoidance) of specific descriptive terms — compensation, incentives, inducements, payments, reimbursements, and rewards. They are rightly concerned that if incentives are too high individuals may volunteer because of fiscal coercion; therefore, IRBs usually direct that children/families be given only nominal sums or token gifts for participating in research-related activities. Researchers are normally allowed to reimburse research subjects for their expenses incurred as part of the project, as for example when participants collect duplicate diet samples.

The dilemma for researchers is that reasonable incentives are often necessary to encourage children/families to volunteer and to complete research-related activities. This is because many exposure assessment studies require participants to put up with inconveniences (e.g., home visits by field staff) and to spend significant time and effort completing monitoring protocols (e.g., recording data on time–activity patterns). In addition to financial incentives for families and children, relatively inexpensive age-specific incentives, such as colored pencils and yo-yos, have been used by several studies to encourage participation and compliance with study protocols (Adgate et al., 2000; Fenske

et al., 2000a; O'Rourke et al., 2000; Sexton et al., 2000). Without adequate incentives, children and families may be less likely to volunteer for exposure assessment studies and to complete monitoring protocols that are burdensome (e.g., wearing personal monitors and maintaining time–activity diaries for 24–48 h) and relatively invasive (e.g., providing blood and urine samples). This issue is especially critical for probability-based exposure studies, which need a reasonably high response (enrollment) rate to ensure that the sample is representative of the population being studied.

Involving Neighborhoods and Communities For some exposure-assessment studies it is important to obtain buy-in and support from members of local neighborhoods and communities. The goal is to inform and educate residents about the study (e.g., explain goals and objectives, answer questions and respond to concerns) and to seek their backing and assistance in carrying it out (e.g., help with recruitment of volunteers, retention of research subjects, and communication of results). As a first step toward promoting involvement, researchers should analyze the situation to obtain a neighborhood/community profile (Finnegan and Sexton, 1999) that provides information about (1) sociodemographic characteristics of residents (e.g., socioeconomic status, ethnicity) and insight into the local social structure (e.g., key public and private organizations, local leaders), (2) power and influence relationships (e.g., understanding of how leaders and organizations operate to manage conflict and competition, allocate resources, and implement public policies), and (3) environmental health realities and perceptions (e.g., local environmental health problems and residents' perceptions of problems). Researchers should use the knowledge gained from the profile to assist them in working cooperatively with members of relevant neighborhoods and communities to build mutual trust, publicize the study, and encourage participation.

A relatively recent development in the field of environmental health, and particularly in the area of exposure assessment, is the concept of "community-based research" (Brown and Vega, 1996; Mason and Boutillier, 1996; Israel et al., 1998). This idea has gained credence in recent years, especially within federal agencies (e.g., EPA, National Institute of Environmental Health Sciences (NIEHS), and the Centers for Disease Control and Prevention (CDC)) and among social scientists, despite the fact that there is currently no consensus-derived definition nor is there general agreement about a normative model for conducting community-based research. Community-based research requires that researchers give up some control over the research process in order to gain direct access to the experience, knowledge, and resources of community members, who function as partners in the research endeavor. The rationale underpinning this approach is typically twofold: (1) it is a way to bridge the sometimes significant gap between environmental health knowledge (research) and its application (practical use in the neighborhood or community); and (2) it provides a strategy to address power imbalances between researchers and research subjects.

Community-based research does not constitute a new and distinctive method for exposure-related research, but rather represents a more holistic research approach that focuses needed attention on the cultural, economic, political, and social aspects of environmental health. At its core, community-based research aims to create a cooperative partnership between researchers and members of neighborhoods/communities expressly for the purpose of improving the health and well being of residents through collaborative research. It is important to remember that not every exposure assessment study can be or should be community-based, and researchers must distinguish between those situations where community-based research is appropriate and where it is not.

To be deemed community-based, an exposure assessment study must meet at least two conditions. First, it must occur within circumscribed geographical and sociopolitical boundaries, which is to say the research must focus on a particular place(s) or setting(s). Second and more significantly, residents must be actively engaged and meaningfully involved in important aspects of the research process, which means that researchers have to share responsibility for identifying research issues, designing and implementing field studies, communicating results, and translating knowledge gained into public health action. By its very nature, therefore, community-based research fosters more equitable distribution of power while at the same time promoting research that is more directly responsive to neighborhood/community needs and concerns.

It is becoming increasingly important for researchers and others involved with assessing children's environmental exposure to become familiar with the principles of community-based research. They should comprehend the opportunities as well as the challenges of putting these principles into practice.

Communicating Results to Study Participants Improvements in measurement technology and analytical methods now afford opportunities for practical and affordable exposure assessments based on relatively in-depth and broad-based monitoring of children and adults. For example, the National Human Exposure Assessment Survey (NHEXAS) studies in Arizona (O'Rourke et al., 2000), the Upper Midwest (EPA Region 5) (Pellizzari et al., 1995), and a special pesticides study in Minnesota (Adgate et al., 2000; Quackenboss et al., 2000) provide cross-sectional data on multipathway exposures to multiple hazardous chemicals for probability-based samples of local

residents, including children (Sexton, 1995). The extent of exposure-related information collected for each research participant is unprecedented, both in terms of breadth (tens to hundreds of individual chemicals) and depth (combination of environmental, personal, and biological samples). A key aspect of the NHEXAS studies and many other exposure studies is a commitment by investigators to communicate findings back to the study participants, including an individualized summary of his or her monitoring results. Although not always acknowledged by investigators, it seems to us that there is, in most instances, an explicit or implicit "social contract" between researchers and research subjects, which stipulates that the experts will attempt, within the constraints of existing knowledge, to interpret the health significance, if any, of measured exposure values. However, with notable exceptions such as lead (Pb) and carbon monoxide (CO), there are few health-derived "bright lines" that allow investigators to construe unambiguously the health implications of an individual's nonoccupational exposures to relatively low levels of toxic chemicals. The situation becomes immensely more complicated when experts try to use short-term exposure measures (e.g., hours, days) to estimate related long-term health consequences (e.g., years, decades, lifetime).

Thus researchers and exposure assessors often find themselves caught in a conundrum. They want to fulfill their social contract with study participants by providing them with information that is accurate, understandable, and useful. But they also want the information to be factual, scientifically credible, balanced, and accompanied by appropriate caveats regarding scientific uncertainty. Perhaps most importantly, they want to avoid causing needless concern or alarm when it is not warranted by the data. Yet people want answers — they particularly want the experts to answer a fundamental question — is it safe? These individuals have, after all, voluntarily participated in an intrusive research project and completed sometimes-demanding study protocols. They have a right to ask the investigators not only to communicate exposure results, but also to provide some health-based context for interpreting measured levels. The problem for investigators is that in most instances there is a scarcity of scientific knowledge and understanding, which limits their ability to infer health-related relevance with an acceptable degree of certainty.

The whole topic of risk communication is a difficult one, and the evidence suggests that effective communication is both an art and a science (NRC, 1989c; Hance et al., 1990; Bennett and Calman, 1999). The next generation of children's exposure studies, which are currently underway, raise complicated questions about how best to communicate extensive "personalized" exposure information to study participants and other interested parties. Researchers should confront these issues early on, working with neighborhoods, communities, and study participants to jointly decide how findings are to be communicated to ensure accuracy, scientific credibility, and privacy, while at the same time providing recipients with easy-to-understand and easy-to-use information.

Data-Collection Issues

This section briefly examines some of the common challenges that confront researchers as they try to collect exposure-related data for children. The emphasis is on quantitative data-collection activities conducted as part of exposure monitoring field studies. Because childhood exposure studies are conducted for a variety of reasons (see Figure 2) using distinct exposure assessment approaches (e.g., direct measurements, reconstructive analysis, or scenario-based evaluation), the following discussion necessarily focuses on identification of key challenges rather than on trying to propose specific solutions. For project-specific information on resolving important data-collection issues, the reader is encouraged to review several articles published as part of this special issue (see, for example, Adgate et al., 2000; Buckley et al., 2000; Fenske et al., 2000a; Jordan et al., 2000; Melnyk et al., 2000; O'Rourke et al., 2000; Sexton et al., 2000).

Identifying and Recruiting Children/Families One of the first issues confronting researchers is the need to answer a fundamental question: How should families with age-eligible children be identified and recruited into the study? Generally speaking, investigators must choose, based on a determination of how best to achieve the study's objectives, between (1) a probability-based sampling frame or (2) a "convenience" (or nonprobability-based) sampling frame. Both approaches typically begin with identification of the exposures (e.g., pesticides), geographical area (e.g., agricultural community), and population of interest (e.g., elementary-school-age children), followed by implementation of recruitment procedures designed to obtain the requisite sample in a timely and cost-effective manner.

If a convenience sample is adequate to meet study objectives, then investigators do not have to worry about probabilistic sampling issues, and can use expedient and relatively inexpensive methods for (1) identifying potential study participants (e.g., obtain contact information from health clinics) and (2) recruiting children/families (e.g., enroll those who meet eligibility requirements and volunteer). For example, Fenske et al. (2000a) examined children's pesticide exposures using a convenience sample obtained through local WIC (Women, Infants, and Children) clinics in an apple-growing region of Washington. Jordan et al. (2000) used a convenience sample to study children's lead (Pb) exposures and

related neurobehavioral effects by recruiting women either prenatally or during their offspring's infancy through health clinics in an economically disadvantaged neighborhood. Melnyk et al. (2000) studied children's dietary exposures in Pb-laden residential environments using a convenience sample of children/families recruited through a state treatment program for lead-exposed children.

Sometimes it is important to obtain a statistically "representative" sample for a particular geographic area or population so that results from the sample (i.e., research subjects) can be used to make quantitative inferences beyond the study. To meet this requirement, investigators must use a probability-based sampling design, which typically means choosing a stratified-random sampling scheme to identify and recruit study participants (e.g., stratified according to gender, age, ethnicity). There are substantial challenges associated with probabilistic sampling for exposure monitoring studies (e.g., that both spatial and temporal sampling must be considered, that the degree of clustering for important exposure-related attributes affects effective sample size, that nonresponse bias can affect results), many of which have been described previously (Callahan et al., 1995).

Attempts to study more-exposed or more-susceptible populations, such as children, the elderly, or the infirm, tend to magnify and exacerbate probability-based sampling problems. For example, random-digit-dialing approaches are a commonly-used, cost-effective method for probabilistic recruiting; however, they can be inefficient and prohibitively expensive for children's exposure studies because a large proportion of households do not have age-eligible children, and certain socioeconomic groups (e.g., poor inner-city families) either do not have telephones or change numbers frequently. Yet despite a plethora of potential problems, several recent exposure-monitoring studies have demonstrated that it is both practical and affordable to obtain probability-based samples of children. Adgate et al. (2000) used a cross-sectional design and a stratified-random sampling format to identify households with age-eligible children, and to screen them so those likely to have higher residential pesticide exposures could be over-sampled. Sexton et al. (2000) employed a stratified-random sampling strategy to assess children's exposure to complex chemical mixtures in economically disadvantaged neighborhoods.

Measuring Children's Exposure/Dose Researchers attempting to use direct (e.g., individual breathing-zone dosimeters) or indirect (e.g., area monitoring in important microenvironments combined with time–activity data) measurement methods to assess children's actual exposures are confronted with numerous challenges. Younger children, including infants, toddlers, and children of elementary school age (see Table 1) cannot be relied on to complete simple monitoring protocols or answer even uncomplicated questions about time spent in exposure-related activities. Researchers must therefore depend on caregivers, teachers, or study technicians to provide assistance with collection of valid direct/indirect measurements of exposure for children who are younger than about 12 years. Two recent studies have demonstrated that, with appropriate safeguards, direct/indirect methods can be used successfully for assessment of (1) pesticide and volatile organic compound (VOC) exposure for children 3–13 years of age (Adgate et al., 2000), and (2) VOC exposure for children 6–12 years old (Sexton et al., 2000).

As Buckley et al. (2000) point out, virtually all children's exposure studies necessarily involve collection of observational information. The utility of exposure monitoring data, especially for younger children, is often directly related to observational feedback from the field technicians who collected it and/or interviews with observant parents. Observing toddlers in their natural environment, scrutinizing their behavior (e.g., licking or mouthing objects such as pets, toys, or household surfaces), and documenting their time–activity patterns (e.g., analyzing videotaped behaviors and activities) are important techniques for identifying important exposure pathways and routes as well as for evaluating the effectiveness of sampling protocols. For many children's exposure studies, observations by all parties involved, including parents, older siblings, teachers, field staff, and investigators, are the key to ensuring both the validity and the value of the data collected.

An increasing number of children's exposure studies involve measurement of biological exposure markers in human tissues (e.g., blood) or excreta (e.g., urine) to characterize internal dose (body burden) and document that exposures have occurred. It is always a challenge to obtain both parental/guardian consent and the child's assent to collect blood samples and, to a lesser extent, urine samples. Parental/guardian concerns about privacy and data-handling issues, unauthorized use of the data, and possible injury or illness due to a needle stick are all reasons that sometimes make it difficult to obtain permission for biological sampling. The actual collection of blood samples depends directly not only on the amount and method of drawing blood (e.g., a few drops by finger stick *versus* tens of milliliters by venipuncture), but also on the ability and personality of the individual drawing the blood. Best results for venipuncture samples are obtained when a trained pediatric phlebotomist takes the sample quickly and painlessly, while reassuring the child and putting him or her at ease. Several recent studies have used biomarkers in blood to assess children's exposure to environmental toxicants (Adgate et al., 2000; Jordan et al., 2000; Sexton et al., 2000).

Most childhood exposure studies that collect urine samples involve children 3 years or older because it is difficult to collect urine sample from younger children. It is usually not feasible to collect a first-morning-void sample, so investigators often settle for taking a sample whenever it is convenient, typically in the morning. It is important for children to feel comfortable and have adequate privacy so they are at ease. The presence of a familiar and trusted person, such as a parent or school nurse, often reassures younger children and can provide a validity check on the samples. Several studies have recently used urinary biomarkers to assess children's exposure to pesticides (Adgate et al., 2000; Aprea et al., 2000; Fenske et al., 2000a,b; O'Rourke et al., 2000; Sexton et al., 2000).

Issues Related to Chemical Analysis of Biological Samples

No matter what the research objectives (Figure 2) or which quantitative exposure assessment approaches (i.e., exposure measurements, reconstructive analysis, and scenario-based evaluation) are used, studies to characterize children's exposure typically require chemical analysis of a particular matrix (e.g., environmental — air, water, food, dust, soil; or biological — blood, hair, saliva, urine) for a toxicant or its derivative. When environmental samples are used as part of the exposure assessment, as in the case of indirect measurement and scenario-based analysis, there is little, if any difference between the chemical analyses of environmental samples for children versus adults. For example, when the primary route of exposure for a given toxicant (e.g., atrazine) is thought to be the consumption of well water, the chemical analysis methods for water samples are the same whether we are concerned about exposure for adults or children (Raymer et al., 2000). On the other hand, when analysis of biological specimens (e.g., human tissue or excreta) is required, as in the case of reconstructive exposure assessment, chemical-analysis issues can vary significantly between adults and children. For example, although a blood sample of 5–10 ml may be necessary for a particular chemical analytical procedure (e.g., determination of blood-VOC levels), it may not be feasible or practical to collect that much blood from an infant or young toddler. Because of the increasing importance of biological markers for assessing children's exposure and the corresponding significance of related chemical-analysis issues, the remainder of this section is devoted to discussing the analytical implications of the type and amount of biological specimens that are available from children.

When human exposure assessment involves biological samples, researchers generally measure the "internal dose," which is the concentration of the toxicant, its primary metabolite(s), or its reaction products (such as adducts) in a biological specimen, such as blood (or its components) or in urine (Pirkle et al., 1995). The choice of a specimen for measuring the internal dose is based primarily on the chemical and physical properties of the toxicant and, in some cases, on the time interval since the last exposure. Highly lipophilic compounds, such as dioxins, polychlorinated biphenyls, and organochlorine pesticides, tend to have long biological half-lives (and are therefore referred to as persistent compounds) and to sequester in the lipid portions of the body, such as adipose tissue. Blood flow through the adipose tissue allows the lipophilic toxicant to equilibrate between the lipids in adipose tissue and the lipids in blood. This equilibration is exemplified by the 1:1 partitioning of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin in humans between the lipids in adipose tissue and the lipids in serum (Patterson et al., 1988). Thus, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin can be measured in either adipose tissue or in serum, with serum being the more readily accessible biological specimen. Concentrations of lipophilic chemicals are generally reported based on their amount in the entire matrix (whole weight) or in the lipid portion (lipid-adjusted).

Lipophobic compounds (referred to as nonpersistent compounds), on the other hand, including many of the organophosphate pesticides, have relatively short biological half-lives and tend to metabolize rapidly to form even more highly lipophobic compounds that are excreted in the urine. Therefore, analysis of urine is generally used for assessing exposure to nonpersistent toxicants. Concentrations of these chemicals are reported based on their amount in the urine specimen or on an adjusted basis (e.g., creatinine adjusted, specific gravity, or osmolality). Some toxicants, such as pentachlorophenol, have both a lipophilic moiety and a lipophobic moiety, and exposure to such toxicants has been assessed in blood and urine (Cline et al., 1989). Likewise, exposure to many VOCs has been assessed by measuring levels in blood and breath and by measuring their metabolites in urine (Brugnone et al., 1989; Ashley et al., 1992).

The time interval since the last exposure can also play a major role in determining the matrix of choice among the

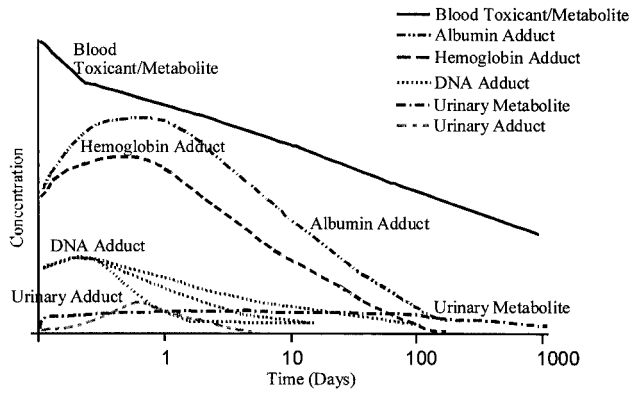

Figure 3. Post-exposure fate of a persistent toxicant in blood and urine.

commonly used matrices (i.e., blood and urine) for assessing exposure to environmental toxicants, especially those that are nonpersistent. This is shown schematically in Figure 3 for a hypothetical persistent toxicant and in Figure 4 for a hypothetical nonpersistent toxicant. The major differences in these two figures are the relative concentrations of the metabolites of the persistent versus the nonpersistent toxicant in blood and urine. The persistent toxicant has a longer half-life in blood, whereas the nonpersistent toxicant is present in blood in appreciable concentrations for a relatively short interval (24 h or less). In contrast, the persistent toxicant does not form urinary metabolites to an appreciable degree, while the nonpersistent toxicant does. These figures illustrate the reasons that persistent toxicants are typically measured in blood and nonpersistent toxicants are measured in urine. However, even nonpersistent toxicants can be measured in blood (a) if the sample is collected soon after exposure or (b) if the method has sufficient sensitivity to measure the small portion of the nonpersistent toxicant that is in the blood for several days after the exposure. The analysis of blood for VOCs at the parts-per-trillion levels by purge-and-trap/mass spectrometry is an example of the latter (Ashley et al., 1992).

Figures 3 and 4 show that various adducts may form between blood components and toxicants, both persistent and nonpersistent. However, adduct-forming toxicants or their metabolites are limited to those that have an electrophilic center, which reacts with the nucleophilic centers of nucleic acids (such as DNA) and proteins (such as hemoglobin and albumin). The use of adducts for assessing the risk of tobacco smoke exposure to children and the developing fetus has been reviewed by Whyatt and Perera (1995). Protein adducts have generally been preferred over DNA adducts for biomonitoring primarily because of the greater sensitivity obtained from protein adducts over a longer post-exposure time period (EPA, 1989). This increased sensitivity is due to the increased amounts of the proteins relative to DNA — in 10 ml of blood there are gram amounts of hemoglobin and albumin whereas only about 1 mg of leukocyte DNA is present. The half-life of the protein adducts is generally longer than that of the DNA adducts because of DNA-repair mechanisms (which vary among cell types and adducts) followed by excretion, although the half-life for certain polyaromatic hydrocarbon–DNA adducts is about 4 months (Mooney et al., 1995). It is important to keep in mind that the curves presented in Figures 3 and 4 are hypothetical; data for hazardous environmental chemicals that children are likely to come into contact with are not always so clear-cut.

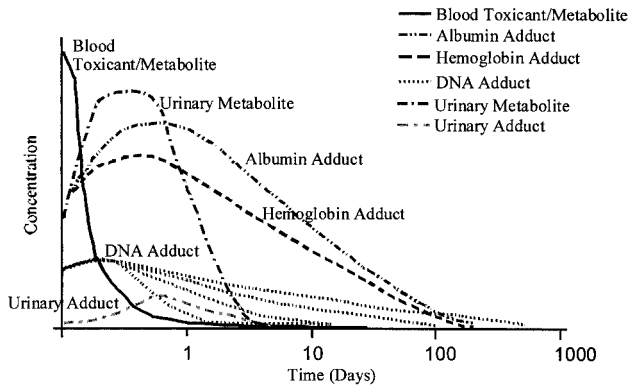

Figure 4. Post-exposure fate of a nonpersistent toxicant in blood and urine.

Of the two proteins (albumin and hemoglobin) normally used for biomonitoring, hemoglobin is generally preferred for a variety of reasons, although the absolute analytical sensitivities for both types of adducts vary with the toxicant (EPA, 1989). Figures 3 and 4 show the potential formation of hemoglobin adducts and their demise with the death of the red blood cell, which has a lifespan of approximately 120 days. Adducts can also form with albumin, the most abundant serum protein. These albumin adducts decay with the decay of albumin, which has an average half-life of 14–20 days. But serum albumin can be lost at a much faster rate in response to gastrointestinal disease, nephrosis, or severe burns. In addition, in the presence of the rare disorder analbuminemia, serum albumin is lacking entirely (EPA, 1989). As analytical methods become even more sensitive, it will be possible to monitor blood adducts of persistent toxicants over a longer post-exposure time period because of the equilibrium of the toxicant between the lipids in adipose tissue and blood. Thus, as the toxicant in blood forms its respective adduct, more of the toxicant becomes available from the adipose tissue, which in turn allows more adduct to form in the blood. Urinary adducts have not been utilized to a great extent in biomonitoring, although nucleic acid adducts have been monitored in urine for assessing exposure to several carcinogens (Shuker and Farmer, 1992; Poirier et al., 2000).

In addition to deciding on the appropriate analytical matrix, the investigator must also consider how much of that matrix is available (the amount being directly related to the child's age) and how much is needed for assessing exposure to environmental toxicants. For example, in the exposure-monitoring portion of the current National Human and Nutrition Examination Survey (NHANES), urine samples are collected for participants who are 6 years of age and older. Although collection of urine is usually thought of as a noninvasive procedure, urine is not collected from preschool children in this large survey because of practical difficulties obtaining adequate samples. As part of NHANES, a complete blood sample (102 ml) is drawn

from all persons 12 years of age or older. Lesser amounts are drawn for children younger than 12 years depending on their age: 1–2 years — 9 ml; 3–5 years — 22 ml; and 6–11 years — 38 ml. For children younger than 12 years old, only lead, cadmium, total mercury, and inorganic mercury are measured for those 1–3 years of age; these elements plus cotinine in serum are measured for those 3 years and older.

Examples of state-of-the-art chemical analyses of biological matrices, including the amount of sample needed and the limit of detection of the analytical method, are provided in Tables 2–6. A list of 28 of the 39 organophosphate pesticides approved by the U.S. Environmental Protection Agency (EPA) for agricultural use and their corresponding phosphorus-containing urinary metabolites is shown in Table 2. These metabolites are nonspecific for a given organophosphate pesticide, but their quantification provides important information about cumulative exposure/dose for this group of pesticides. Measurement of these metabolites began in the first year (1999) of the current NHANES and will continue in this statistically representative sample of the U.S. population. Measured values will be reported as part of the National Exposure Report Card, which will be updated annually using the Internet.

Table 3 provides a listing of nonpersistent pesticides that can be measured in urine. Some of these were measured in a subset of adults from NHANES III (Hill et al., 1995a). The current list of pesticides includes representatives of the organophosphate, carbamate, amide, carboxylic acid, phenol, pyrethroid, aromatic, and triazine classes. In most cases, the metabolite is the analyte that is measured in the urine. The analytical technique is either gas chromatography/mass spectrometry/mass spectrometry (GC/MS/MS) or liquid chromatography/mass spectrometry/mass spectrometry (LC/MS/MS). With the exception of deltamethrin and

Table 2. Organophosphate pesticides and their phosphorus-containing metabolites (LOD in ng/ml for 4 ml urine sample).[a]

Pesticide	DMP (0.51)	DMPT (0.18)	DMDTP (0.08)	DEP (0.2)	DEPT (0.09)	DEDTP (0.05)
Azinphos methyl	X	X	X			
Chlorethoxyphos				X	X	
Chlorpyrifos				X	X	
Chlorpyrifos methyl	X	X				
Coumaphos				X	X	
Dichlorvos (DDVP)	X					
Diazinon				X	X	
Dicrotophos	X					
Dimethoate	X	X	X			
Disulfoton				X	X	X
Ethion				X	X	X
Fenitrothion	X	X				
Fenthion	X	X				
Isazaphos-methyl	X	X				
Malathion	X	X	X			
Methidathion	X	X	X			
Methyl parathion	X	X				
Naled	X					
Oxydemeton-methyl	X	X				
Parathion				X	X	
Phorate				X	X	X
Phosmet	X	X	X			
Pirimiphos-methyl	X	X				
Sulfotepp				X	X	
Temephos	X	X				
Terbufos				X	X	X
Tetrachlorvinphos	X					
Trichlorfon	X					

LOD = limit of Detection; DMP = dimethylphosphate; DMPT = dimethylthiophosphate; DMDTP = dimethyldithiophosphate; DEP = diethylphosphate; DEPT = diethylthiophosphate; DEDTP = diethyldithiophosphate.

[a]Book of Analytical Procedures. Toxicology Branch, DLS, CDC: Volume II, Chapter 4.

Table 3. List of nonpersistent pesticides monitored in urine at the National Center for Environmental Health.

Pesticide	Analyte	Urine volume (ml)	LOD (ng/ml)	References
Chlorpyrifos; Chlorpyrifos-methyl	3,5,6-Trichloro-2-pyridinol[a]	10	1.3	Hill et al., 1995b
Diazinon	Oxypyrimidine	10	0.02	Baker et al., 2000
Malathion	Malathion diacid	10	0.3	Beeson et al., 1999
Parathion; Methyl parathion	4-Nitrophenol	3	0.1	Footnote 1
Carbaryl	1-Naphthol[a]	10	1.4	Hill et al., 1995b
Carbofuran	Carbofuranphenol[a]	10	1	Hill et al., 1995b
Propoxur	2-Isopropoxyphenol[a]	10	1	Hill et al., 1995b
Acetochlor	Acetochlor mercapturate	5	1	Footnote 2
Alachlor	Alachlor mercapturate	10	15	Footnote 2
Metolachlor	Metolachlor mercapturate	5	1	Footnote 2
DEET	*N,N*-Diethyltoluamide (DEET)	5	0.05	Footnote 2
2,4-D, esters, salts	2,4-Dichlorophenoxyacetic acid (2,4-D)	10	0.3	Beeson et al., 1999
2,4,5-T, esters, salts	2,4,5-Trichlorophenoxyacetic acid (2,4,5-T)	10	0.3	Footnote 2
Dicamba	Dicamba[a]	10	0.5	Shealy et al., 1996
Pentachlorophenol	Pentachlorophenol[a]	5	1	Hill et al., 1995b
o-Phenylphenol	*o*-Phenylphenol	5	2	Footnote 2
Synthetic pyrethroids	3-Phenoxybenzoic acid	10	0.5	Baker et al., 2000
Deltamethrin	*cis*-3-(2,2-Dibromovinyl)-2,2-dimethylcyclopropanecarboxylic acid	2.5	0.5	Footnote 3
Permethrin	*cis/trans*-3-(2,2-Dichlorovinyl)-2,2-dimethylcyclopropanecarboxylic acid	2.5	0.5	Footnote 3
Naphthalene	1-Naphthol, 2-naphthol[a]	10	1.4	Hill et al., 1995b
1,4-Dichlorobenzene	2,5-Dichlorophenol			Footnote 2 and Hill et al., 1995b
Atrazine	Atrazine mercapturate	10	0.3	Beeson et al., 1999

LOD = limit of detection.
[a]Measured by gas chromatography/mass spectrometry/mass spectrometry (GC/MS/MS); all others, by liquid chromatography/MS/MS.
Footnotes 1, 2, and 3 from Book of Analytical Procedures. Toxicology Branch, DLS, CDC: Volume II, Chapters 3, 5 and 6, respectively.

permethrin, all of the analytes measured by LC/MS/MS can be quantified in a single 5-ml sample of urine (Baker et al., 2000).

Table 4 lists other nonpersistent organic toxicants that are being measured in the current NHANES. These include two groups of potential endocrine modulators: the synthetic phthalates (widely used as plasticizers in plastics, particularly polyvinyl chloride) and the naturally occurring phytoestrogens. Blount et al. (2000) described the specific phthalates (monitored as their monocarboxylic acid metabolite), and Valentin-Blasini et al. (2000) described the specific phytoestrogens that are

Table 4. List of other groups of nonpersistent toxicants measured at the National Center for Environmental Health.

Toxicant group	Analytes (number)	Matrix	Volume (ml)	LOD (ng/ml)	References
Phthalates	Monocarboxylic Acids (8)[a]	U	1	1	Blount et al., 2000
Phytoestrogens	Phytoestrogens/metabolites (7)[a]	U, S	1	0.2–4 (U)	Valentin-Blasini et al., 2000
Volatile organic compounds	VOCs (32)[a]	WB	5	0.005–0.07	Ashley et al., 1992
Selected VOCs; e.g., ethylene oxide, vinyl chloride	*N*-Acetyl-*S*-(2-hydroxyethyl)-L-cysteine	U	1	0.68	Barr and Ashley, 1998
Environmental tobacco smoke	Cotinine	S, U, Sa	1	0.05	Bernert et al., 1997,2000
	Nicotine/metabolites (6)[a]	U	1	0.01	Footnote 1
	4-Methylnitrosoamino-1-(3-pyridyl)-1-butanol (NNAL)	U	5	6×10^{-4}	Footnote 2

[a]Values in parentheses are the number of analytes measured.
LOD = limit of detection; U = urine; S = serum; WB = whole blood; Sa = saliva. Footnotes 1 and 2 from Book of Analytical Procedures. Air Toxicant Branch, DLS, CDC: Volume I, Chapters 5 and 6, respectively.

Table 5. List of persistent organic pollutants by class measured in serum at the National Center for Environmental Health.

Toxicant (by class)	Serum volume (ml)	LOD (approximate) (ng/ml)	References
Polychlorodibenzo-*p*-dioxins (7 congeners)	10	$(15 \text{ to } 430)\times10^{-6}$	DiPietro et al., 1997
Polychlorodibenzofurans (10 congeners)	10	15×10^{-6}	DiPietro et al., 1997
Coplanar polychlorinated biphenyls (4 congeners)	10	65×10^{-6}	DiPietro et al., 1997
Polychlorinated biphenyls (37 isomers)	1	0.05–0.32	DiPietro et al., 1997
Organochlorine pesticides (12 compounds)	1	0.07–0.26	DiPietro et al., 1997

LOD = limit of detection.

measured as part of NHANES. A summary of analytical results for 32 VOCs measured in blood from a subset of adults in NHANES III has been published previously (Ashley et al., 1994).

Table 5 lists persistent chemicals that can be measured in serum. The chemicals include polychlorinated dibenzo-*p*-dioxins, polychlorinated dibenzofurans, polychlorinated biphenyls (PCBs), and organochlorine pesticides that have long half-lives in the body. Reference range concentrations (i.e., baseline exposure/dose distributions) for many of these chemicals were reported by Needham et al. (1996), and these data will be updated as part of the National Exposure Report Card.

Table 6 summarizes analytical information for 21 chemical elements that can be measured in biological matrices. Of particular note is the method using inductively coupled argon plasma/mass spectrometry, which is capable of concurrent measurement of 14 elements in a single urine sample. Levels of many of these chemical elements and many organic toxicants have been measured as part of NHANES, and as part of collaborative studies between the NCEH/CDC and the Agency for Toxic Substances and Disease Registry (ATSDR) (e.g., exposure assessments for populations living near Superfund sites); EPA (e.g., NHEXAS, the Science to Achieve Results (STAR) grants program, and U.S./Mexico border program); NIEHS (e.g.,

Table 6. List of elements measured at the National Center for Environmental Health.

Toxicant	Matrix	Amount (ml)	LOD (ng/ml)	Method	References
Lead[a]	WB	0.1	4.0	AAS	Miller et al., 1987
Cadmium[a]	WB	0.1	0.3	AAS	Stoeppler and Brandt, 1980
Mercury (total)	WB	0.1	0.14	AAS	Greenwood et al., 1977
Mercury (inorganic)	WB	0.1	0.45	AAS	Greenwood et al., 1977
Selenium	S	0.05	2.0	AAS	Lewis et al., 1986
Arsenic	U	0.10	4.0	AAS	Paschal et al., 1986
Mercury	U	0.10	0.2	AAS	Littlejohn et al., 1976
Nickel	U	0.10	0.4	AAS	Paschal and Bailey, 1989
Chromium	U	0.10	0.4	AAS	Paschal and Bailey, 1991
Barium[b]	U	0.10	0.12	ICP/MS	Paschal et al., 1998
Beryllium[b]	U	0.10	0.13	ICP/MS	Paschal et al., 1998
Cadmium[b]	U	0.10	0.06	ICP/MS	Paschal et al., 1998
Cobalt[b]	U	0.10	0.07	ICP/MS	Paschal et al., 1998
Cesium[b]	U	0.10	0.14	ICP/MS	Paschal et al., 1998
Lead[b]	U	0.10	0.10	ICP/MS	Paschal et al., 1998
Molybdenum[b]	U	0.10	0.80	ICP/MS	Paschal et al., 1998
Platinum[b]	U	0.10	0.04	ICP/MS	Paschal et al., 1998
Antimony[b]	U	0.10	0.04	ICP/MS	Paschal et al., 1998
Thallium[b]	U	0.10	0.02	ICP/MS	Paschal et al., 1998
Tungsten[b]	U	0.10	0.04	ICP/MS	Paschal et al., 1998
Thorium[b]	U	0.10	0.006	ICP/MS	Paschal et al., 1998
Uranium[b]	U	0.10	0.004	ICP/MS	Ting et al., 1996
Iodine	U	0.10	3.0	ICP/MS	Fecher et al., 1998

AAS = atomic absorption spectroscopy; ICP/MS = inductively coupled plasma/mass spectrometry; S = serum; U = urine; WB = whole blood.
[a]Measured simultaneously in 0.1 ml of whole blood.
[b]Measured simultaneously in 0.1 ml of urine.

Superfund programs, National Toxicology Program); and with four of the eight Children's Environmental Health and Disease Prevention Centers (i.e., University of California-Berkeley, University of Washington, Columbia University, and Mt. Sinai School of Medicine), which are sponsored by EPA, NIEHS, and CDC.

The primary matrices used in all of these studies were urine and blood. Children 12 years of age and older are usually sampled much like adults in terms of the matrix and the amount of that matrix that can be collected. However, the type and amount of matrices that can be collected are an important issue for younger children, particularly for embryos, fetuses, infants, and toddlers (Dimandja et al., 2000; Phillips, 2000). Yet accurate exposure assessment is especially important during these early years because of numerous windows of vulnerability and times of special sensitivities to environmental toxicants (see Table 1). For fetal exposure, there is no known biological matrix that can be monitored to reflect all potentially susceptible time periods, although meconium may integrate exposures from about 16 weeks gestation until after delivery (Moriya et al., 1994). In addition to meconium, amniotic fluid (generally taken early in the second trimester), umbilical cord material, cord blood, postnatal blood spots from finger or heel sticks, and hair have been used to assess prenatal and early postnatal exposures (Burse et al., 2000; Korrick et al., 2000). Hair from the mother has also been used to assess fetal exposure because the levels of certain toxicants in specific lengths of hair reflect maternal exposures during specific parts of the gestational period (Grandjean et al., 1992). These hair levels may also reflect the maternal blood levels of these toxicants, which can pass through the placenta and into the fetus (Paschal et al., 1989). Although each of these matrices has certain advantages and disadvantages, none of them accurately reflect toxicant levels during the entire gestational period.

Infancy is the next stage of development (Table 1) and for children who are being breastfed the ingestion of mother's milk is the major route of exposure to many environmental toxicants, especially those that are lipophilic (Anderson and Wolff, 2000). The primary means of assessing exposure for these children is through analysis of their mothers' milk coupled with the lactational history of the infant. Blood spots from finger and heel sticks are another possible matrix. Analysis of blood spots has the advantage of yielding environmental exposure information along with genetic information, which will become of increasing importance as we examine the relation between an individual's environmental exposures and his or her biological susceptibility to an adverse health outcome. However, using blood spots to assess environmental exposures in children will tax the sensitivity of our current methods, although one environmental chemical, *p*,*p*′-DDE, has been measured in blood spots taken at birth (Burse et al., 1997). Urine samples have also been collected from infants using cotton rolls in diapers to absorb urine. The urine was mechanically squeezed from the rolls and analyzed for cotinine, the primary metabolite of nicotine and a biological marker of exposure to environmental tobacco smoke (Matt et al., 1999).

As children enter the toddler period (ages 1 to 3 years), it becomes increasingly practical to collect urine specimens in addition to blood spots. Three methods have been used to collect urine specimens from children not yet potty trained: by using a urine-collection bag, by obtaining urine directly from the diaper, and, as mentioned above, by using cotton inserts inside the diaper (Hu et al., 2000). One potential matrix that is often overlooked in exposure studies involving older infants and toddlers is saliva, which is relatively easy and noninvasive to collect. This technique was recently used to measure cotinine in children, and results indicate that an individual's cotinine levels in serum and saliva are similar (Bernert et al., 2000).

As children develop through the pre-adolescence and adolescence years, there is an increase in both the types of biological specimens available and the amount of sample that can be collected. As mentioned earlier, a child who is 12 years or older is typically considered competent to volunteer to provide a full (adult) complement of biological samples, including urine, blood, and hair.

Regardless of the biological matrix or the amount collected, it must be obtained under prescribed conditions that minimize potential chemical interferences and contamination. Knowledgeable laboratory personnel should be involved in developing the sampling protocol and establishing standard shipping procedures in order to ensure delivery of a "pristine" sample to the laboratory. Likewise, the users of the data should be familiar with the laboratory and its methods as well as the strengths and weaknesses of each.

Once the sample has been collected and placed in a container for shipment to the laboratory, there are no differences in the handling and analysis of samples taken from children or adults. The actual chemical analysis generally consists of three steps — sample preparation, chemical measurement, and data analysis. It is critical that all steps prior to and during the chemical analysis are conducted using all aspects of Good Laboratory Practice. In addition, for analyses of human samples that may be used for diagnostic purposes, the laboratory and its analytical methods must be approved by the Health Care Financing Administration as stated in the Clinical Laboratory Improvement Act (CLIA) of 1988. It is important for investigators to be aware that many laboratories currently analyzing biological samples mistakenly believe they do not need to be CLIA-approved, but if any of their results, including those outside the normal range, are used for case management and diagnosis, that laboratory must be CLIA-approved.

Conclusions

Protection of children's environmental health is an important and longstanding goal for policymakers, regulators, risk assessors, and researchers. Today, safeguarding the health and well-being of this potentially vulnerable and diverse population is not only a principal public health objective but also a national priority. Nevertheless, formulation, implementation, and evaluation of effectual public policies to prevent or reduce childhood exposures to hazardous chemicals are hindered in many cases by a paucity of scientific knowledge and understanding. With few exceptions, there is an acute need for more and better information about sources, fate and transport processes, pathways, exposure concentrations, doses, and related adverse health effects. The current state-of-knowledge and associated research needs for many aspects of children's environmental health have been examined in several recent publications (EHP, 1998a,b,1999,2000; Dearry and Collman, 1999; Rylander and Etzel, 1999; Schneider and Freeman, 2000). One recurring issue is the critical scarcity of accurate exposure-related data for children of all ages, backgrounds, and circumstances; a subject that is the topic of numerous contemporary publications (Mukerjee, 1998; EPA, 1999a; Adgate and Sexton, 2000; Armstrong et al., 2000; EHP, 2000; Hubal et al., 2000b).

Accurate characterization of children's exposure to hazardous environmental chemicals is a necessary, but not sufficient condition for development of related public health policies that are effective, efficient, and equitable. Better and more comprehensive data on childhood exposures are needed to (1) improve health risk assessments, (2) foster informed and reasonable risk management decisions, and (3) provide crucial information that is the foundation of constructive risk communication strategies. Researchers and exposure assessors currently face many challenges and complexities as they strive to design, implement, and interpret scientifically rigorous studies that measure children's actual exposure/dose. This article has examined three categories of factors that can complicate assessment of children's exposure: (1) administrative issues (e.g., obtaining IRB approval, providing adequate incentives for participants, involving neighborhoods and communities, communicating results to participants and other stakeholders); (2) data-collection issues (e.g., identifying and recruiting children/families, measuring actual exposure/dose), and (3) chemical-analysis issues (e.g., dealing with the effects of the child's age on the type and amount of biological samples available for analysis). The goal is to stimulate dialogue among researchers, risk assessors, and policy makers regarding ways to conduct exposure-monitoring studies that are more effective and efficient.

The good news is that the next generation of children's exposure monitoring studies is already underway, using novel and innovative approaches to overcome fundamental obstacles and practical barriers (see, for example, many of the articles in this special issue). Results from these studies promise to provide new insights into conducting exposure-related research on this historically under-studied population, while at the same time improving knowledge and increasing understanding of when, where, why, how, and for whom elevated exposures are likely to occur.

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References

Adgate J.L., and Sexton K. Children's exposure to pesticides in residential settings. In: Handbook of Pesticide Toxicology (R. Krieger, Ed.). Academic Press, San Diego, CA, 2000 (in press).

Adgate J.L., Clayton C.A., Quackenboss J.J., Thomas K.W., Whitmore R.W., Pellizzari E.D., Lioy P.J., Shubat P., Stroebel C., Freeman N.C.G., and Sexton K. Measurement of multi-pollutant and multi-pathway exposures in a probability-based sample of children: practical strategies for effective field studies. *J Exposure Anal Environ Epidemiol* 2000 (this issue).

Akland G.G., Pellizzari E.D., Hu Y., Roberds M., Lecke C.A., and Berry M.R. Factors influencing total dietary exposures of young children. *J Exposure Anal Environ Epidemiol* 2000 (this issue).

Anderson H.A., and Wolff M.S. Environmental contaminants in human milk. *J Exposure Anal Environ Epidemiol* 2000 (this issue).

Aprea C., Strambi M., Novelli M.T., Lunghini L., and Bozzi N. Biologic monitoring of exposure to organophosphorus pesticides in 195 Italian children. *Environ Health Perspect* 2000: 108 (6): 521–525.

Armstrong T.W., Hushka L.J., Tell J.G., and Zaleski R.T. A tiered approach for assessing children's exposure. *Environ Health Perspec* 2000: 108 (6): 469–474.

Ashley D.L., Bonin M.A., Cardinali F.L., McCraw J.M., Holler J.L., Needham L.L., and Patterson D.G. Jr. Determining volatile organic compounds in human blood from a large sample population by using purge and trap gas chromatography/mass spectrometry. *Anal Chem* 1992: 64: 1021–1029.

Ashley D.L., Bonin M.A., Cardinali F.L., McCraw J.M., and Wooten J.V. Blood concentrations of volatile organic compounds in a nonoccupationally exposed US population and in groups with suspected exposure. *Clin Chem* 1994: 40: 1401–1404.

Baker S.E., Barr D.B., Driskell W.J., Beeson M.D., and Needham L.L. Quantification of selected pesticide metabolites in human urine using isotope dilution high-performance liquid chromatography/tandem mass spectrometry. *J Exposure Anal Environ Epidemiol* 2000 (this issue).

Barr D.B., and Ashley D.L. A rapid, sensitive method for the quantification of *N*-acetyl-*S*-(2-hydroxyethyl)-L-cysteine in human urine using isotope-dilution HPLC-MS/MS. *J Anal Toxicol* 1998: 22: 96–104.

Bearer C.F. Environmental health hazards: How children are different from adults. *Future Child: Crit Issues Child Youths* 1995: 5 (2): 11–26.

Bearer C.F. Biomarkers in pediatric environmental health: a cross-cutting issue. *Environ Health Perspect* 1998: 106 (suppl 3): 813–816.

Beeson M.D., Driskell W.J., and Barr D.B. Isotope dilution high performance liquid chromatography/tandem mass spectrometry method for quantifying urinary metabolites of atrazine, malathion, and 2,4-dichlorophenoxyacetic acid. *Anal Chem* 1999: 71: 3526–3530.

Bennett P., and Calman K. Risk Communication and Public Health. Oxford University Press, New York, NY, 1999.

Bernert J.T., McGuffey J.E., Morrison M.A., and Pirkle J.L. Comparison of serum and salivary cotinine measurements by a sensitive high-performance liquid chromatography-tandem mass spectrometry method as an indicator of exposure to tobacco smoke among nonsmokers and nonsmokers. *J Anal Toxicol* 2000: 24: 333–339.

Bernert J.T., Turner W.E., Pirkle J.L., Sosnoff C.S., Akins J.R., Waldrep M.K., Ann Q., Covey T.R., Whitfield W.E., Gunter E.W., Miller B.B., Patterson D.G., Needham L.L., Hannon W.H., and Sampson E.J. Development and validation of a sensitive measurement of serum cotinine in both smokers and nonsmokers by liquid chromatography/atmospheric pressure ionization tandem mass spectrometry. *Clin Chem* 1997: 43: 2281–2291.

Blount B.C., Milgram K.E., Silva M., Malek N., Reidy J.A., Needham L.L., and Brock J.W. Quantitative detection of eight phthalate metabolites in human urine using HPLC-APCIMS/MS. *Anal Chem* 2000: 72: 4127–4134.

Brown L., and Vega W. A protocol for community-based research. *Am J Prev Med* 1996: 12 (4): 4–5.

Brugnone F., Perbellini L., Faccini G.B., Pasini F., Maranelli G., and Romeo L. Breath and blood levels of benzene, toluene, cumene, and styrene in nonoccupational exposure. *Int Arch Occup Environ Health* 1989: 61: 303–311.

Buckley B., Ettinger A., Hore P. Lioy P.J., and Freeman N.C.G. Using observational information to plan and implement field studies with children as research subjects. *J Exposure Anal Environ Epidemiol* 2000 (this issue).

Buffler P.A. Carcinogen risk assessment guidelines and children. *Environ Health Perspect* 1999: 107 (6): A286–A288.

Burse V.W., DeGuzman M.R., Korver M.P., Najam A.R., Williams C.C., Hannon W.H., and Therrell B.L. Preliminary investigation of the use of dried-blood spots for the assessment of *in utero* exposure to environmental pollutants. *Biochem Mol Med* 1997: 61: 236–239.

Burse V.W., Najam A.R., Williams C.C., Korver M.P., Smith B.F., Sam P.M., Young S.L., and Needham L.L. Utilization of umbilical cords to assess *in utero* exposure to persistent pesticides and polychlorinated biphenyls. *J Exposure Anal Environ Epidemiol* 2000 (this issue).

Callahan M.A., Clickner R.P., Whitmore R.W., Graham K., and Sexton K. Overview of important design issues for a national human exposure assessment survey. *J Exposure Anal Environ Epidemiol* 1995: 5 (3): 257–282.

Cline R.E., Hill R.H. Jr., Phillips D.L., and Needham L.L. Pentachlorophenol measurements in body fluids of people in log homes and workplaces. *Arch Environ Contam Toxicol* 1989: 18: 475–481.

Dearry A., and Collman G. (Eds.). Children's environmental health and disease prevention research. *Environ Health Perspect* 1999: 107 (suppl 3): 391–460.

DiPietro E.S., Lapeza C.R. Jr., Cash T.P., Turner W.E., Green V.E., Gill J.B., and Patterson D.G. Jr. A fast universal automated cleanup system for the isotope-dilution high-resolution mass spectrometric analysis of PCDDs, PCDFs, coplanar-PCBs, PCB congeners, and persistent pesticides from the serum sample. *Organohalogen Compd* 1997: 31: 26–31.

Dimandja J.M.D., Grainger J., Patterson D.G., Turner W.E., and Needham L.L. Measurements for assessing environmental exposures to children using small amounts of serum and urine. *J Exposure Anal Environ Epidemiol* 2000 (this issue).

Environmental Health Perspectives (EHP). Preventing child exposures to environmental hazards: research and policy issues. *Environ Health Perspect* 1995: 103 (suppl 6): 3–184.

Environmental Health Perspectives (EHP). Children's environmental health: research, practice, prevention, and policy. *Environ Health Perspect* 1998a: 106 (suppl 3): 785–862.

Environmental Health Perspectives (EHP). Preventable causes of cancer in children. *Environ Health Perspect* 1998b: 106 (suppl 3): 865–925.

Environmental Health Perspectives (EHP). Children's Health Issue. *Environ Health Perspect* 1999: 107 (6): 423–505.

Environmental Health Perspectives (EHP). Developing brain and environment, and critical windows of exposure for children. *Environ Health Perspect* 2000: 108 (suppl 3): 373–597.

Fecher P.A., Goldmann I., and Nagengast A. Determination of iodine in food samples by inductively coupled plasma mass spectrometry after alkaline extraction. *J Anal At Spectrom* 1998: 13: 977–982.

Fenske R.A., Lu C., Simcox N.J., Lowewenherz C., Touchstone J., Moate T.F., Allen E.H., and Kissel J.C. Strategies for assessing children's organophosphate pesticide exposures in agricultural communities. *J Exposure Anal Environ Epidemiol* 2000a (this issue).

Fenske R.A., Kissell J.C., Chensheng L., Kalman D.A., Simcox N.J., Allen E.H., and Keifer M.C. Biologically based pesticide dose estimates for children in an agricultural community. *Environ Health Perspect* 2000b: 108: 515–520.

Finnegan J.R., and Sexton K. Community-based environmental decisions: analyzing power and leadership. In: Better Environmental Decisions: Strategies for Governments, Businesses, and Communities (Sexton K., Marcus A.A., Easter K.W., and Burkhardt T.D., Eds.), Island Press, Washington, DC, 1999, pp. 331–351.

Grandjean P., Weihe P., Jorgensen P.J., Clarkson T., Cernichiari E., and Videro T. Impact of maternal seafood diet on fetal exposure to mercury, selenium, and lead. *Arch Environ Health* 1992: 47: 185–195.

Greenwood M.R., Shahir P., Clarkston T.W., Farant J.P., Chartrand A., and Khayat A. Epidemiological experience with the Magos' reagents in the determination of different forms of mercury in biological samples by flameless atomic absorption. *J Anal Toxicol* 1977: 1: 265–269.

Guzelian P.S., Henry C.J., and Olin S.S. Similarities and Differences between Children and Adults: Implications for Risk Assessment. ILSI Press, Washington, DC, 1992.

Hance B.J., Chess C., and Sandman P.M. Industry Risk Communication Manual. Lewis Publishers, Boca Raton, FL, 1990.

Hill R.H. Jr., Head S.L., Baker S., Gregg M., and Needham L.L. Pesticide residues in urine of adults living in the United States: reference range concentrations. *Environ Res* 1995a: 71: 99–108.

Hill R.H. Jr., Shealy D.B., Head S.L., Williams C.C., Bailey S.L., Gregg M., Baker S.E., and Needham L.L. Determination of pesticide metabolites in human urine using isotope dillution technique and tandem mass spectrometry. *J Anal Toxicol* 1995b: 19: 323–329.

Hu Y., Barr D., Akland G., Melnyk L., Pellizzari E., Raymer J.H., and Roberds J.M. Collecting urine samples from young children using cotton gauze for pesticide studies. *J Exposure Anal Environ Epidemiol* 2000 (this issue).

Hubal E.A.C., Sheldon L.S., Zufall M.J., Burke J.M., and Thomas K.W. The challenge of assessing children's exposure to pesticides. *J Exposure Anal Environ Epidemiol* 2000a (this issue).

Hubal E.A.C., Sheldon L., Burke J.M., McCurdy T.R., Berry M.R., Rigas M.L., Zartarian V., and Freeman N.C.G. Children's exposure assessment: a review of factors influencing children's exposure and the data available to characterize and assess that exposure. *Environ Health Perspect* 2000b: 108 (6): 475–486.

Hulka B.S., Wilcosky T.C., and Griffith J.D. Biological Markers in Epidemiology. Oxford University Press, New York, NY, 1990.

Israel B.A., Schulz A.J., Parker E.A., and Becker A.B. Review of community-based research: assessing partnership approaches to improve public health. *Annu Rev Public Health* 1998: 19: 173–202.

Jordan C., Lee P., and Shapiro E. Measuring developmental outcomes of lead exposure in an urban neighborhood: the challenges of community-based research. *J Exposure Anal Environ Epidemiol* 2000 (this issue).

Kaiser J. No meeting of minds on childhood cancer. *Science* 1999: 286: 1832–1834.

Korrick S.A., Altshul L.M., Tolbert P.E., Burse V.W., Needham L.L., and Monson R.R. Measurement of PCBs, DDE, and hexachlorobenzene in cord blood from infants born in towns adjacent to a PCB-contaminated waste site. *J Exposure Anal Environ Epidemiol* 2000 (this issue).

Landrigan P.J., and Carlson J.E. Environmental policy and children's health. *Future Child: Crit Issues Child Youths* 1995: 5 (2): 34–52.

Lewis S.A., Hardison N.W., and Veillon C. Comparison of isotope dilution mass spectrometry and graphite furnace atomic absorption spectrometry with Zeeman background correction for determination of plasma selenium. *Anal Chem* 1986: 58: 1272–1273.

Littlejohn D., Fell G.S., and Ottaway J.M. Modified determination of total and inorganic mercury in urine by cold vapor atomic absorption spectroscopy. *Clin Chem* 1976: 22: 1719–1723.

Lubin B., and Lewis R. Biomarkers and pediatric environmental health. *Environ Health Perspect* 1995: 103 (suppl 6): 99–104.

Mason R., and Boutillier M. The challenge of genuine power sharing in participatory research: The gap between theory and practice. *Can J Community Ment Health* 1996: 15 (2): 145–151.

Matt G.E., Wahlgren D.R., Hovell M.G., Zakarian J.M., Bernert J.T., Meltzer S.B., Pirkle J.L., and Caudill S. Measuring environmental tobacco smoke exposure in infants and young children through urine cotinine and memory-based parental reports: empirical findings and discussion. *Tob Control* 1999: 8: 282–289.

Melnyk L.J., Berry M.R., Sheldon L.S., Freeman N.C.G., Pellizzari E.D., and Kinman R.N. Dietary exposure of children in lead-laden environments. *J Exposure Anal Environ Epidemiol* 2000 (this issue).

Miller D.T., Paschal D.C., Gunter E.W., Stroud P.E., and D'Angelo J. Determination of lead using electrothermal atomization atomic absorption spectrometry with a L'vov platform and matrix modifier. *Analyst* 1987: 112: 1701–1704.

Mooney L.A., Santella R.M., Covey L., Jeffrey A.M., Bigbee W., Randall M.C., Cooper T.B., Ottman R., Tsai W.Y., Wazneh L., Glassman A.H., Young T.L., and Perera F.P. Decline of DNA damage and other biomarkers in peripheral blood following smoking cessation. *Cancer Epidemiol Biomarkers Prev* 1995: 4: 627–634.

Moriya F., Chan K.M., Noguchi T.T., and Wu P.Y.K. Testing for drugs of abuse in meconium of newborn infants. *J Anal Toxicol* 1994: 18: 41–45.

Mukerjee D. Assessment of risk from multimedia exposures of children to environmental chemicals. *J Air Waste Manage Assoc* 1998: 48: 483–501.

National Research Council (NRC). Biomarkers in Pulmonary Toxicology. National Academy Press, Washington, DC, 1989a.

National Research Council (NRC). Biomarkers in Reproductive Toxicology. National Academy Press, Washington, DC, 1989b.

National Research Council (NRC). Improving Risk Communication. National Academy Press, Washington, DC, 1989c.

National Research Council (NRC). Biological Markers in Immunotoxicology. National Academy Press, Washington, DC, 1992.

National Research Council (NRC). Pesticides in the Diets of Infants and Children. National Academy Press, Washington, DC, 1993.

Needham L.L., Patterson D.G. Jr., Burse V.W., Paschal D.C., Turner W.E., and Hill R.H. Jr. Reference range data for assessing exposure to selected environmental toxicants. *Toxicol Ind Health* 1996: 12: 507–513.

O'Fallon L.R., Collman G.W., and Dearry A. The National Institute of Environmental Health Sciences' research program on children's environmental health. *J Exposure Anal Environ Epidemiol* 2000 (this issue).

O'Rourke M.K., Lizardi P.S., Rogan S.P., Freeman N.C.G., Aquirre A., and Saint C.G. Pesticide exposure and creatinine variation among young children. *J Exposure Anal Environ Epidemiol* 2000 (this issue).

Paschal D.C., and Bailey G.G. Determination of nickel in urine with graphite furnace atomic absorption spectroscopy using Zeeman correction. *Sci Total Environ* 1989: 89: 305–310.

Paschal D.C., and Bailey G.G. Determination of chromium in urine with graphite furnace atomic absorption spectroscopy using Zeeman correction. *At Spectrosc* 1991: 12: 151–154.

Paschal D.C., Kimberly M.M., and Bailey G.G. Determination of urinary arsenic by electrothermal atomic absorption spectrometry with the L'vov platform and matrix modification. *Anal Chim Acta* 1986: 181: 179–186.

Paschal D.C., DiPietro E.S., and Phillips D.L. Age dependence of metals in hair in a selected U.S. population. *Environ Res* 1989: 48: 17–28.

Paschal D.C., Ting B.G., Morrow J.C., Pirkle J.L., Jackson R.J., Sampson E.J., Miller D.T., and Caldwell K.L. Trace metals in urine of United States residents: reference range concentrations. *Environ Res* 1998: 76A: 53–59.

Patterson D.G. Jr., Needham L.L., Pirkle J.L., Roberts D.W., Bagby W.A., Garrett J.S., Andrews J.S. Jr., Falk H., Sampson E.J., and Houk V.W. Correlation between serum and adipose levels of 2,3,7,8-TCDD in 50 persons from Missouri. *Arch Environ Contam Toxicol* 1988: 17: 139–143.

Pellizzari E.D., Lioy P.J., Quackenboss J.J., Whitmore R.W., Clayton A.C., Freeman N.C.G., Waldman J., Thomas K.W., Rhodes C., and Wilcosky T. Population-based exposure measurements in EPA Region 5: a phase 1 field study in support of the National Human Exposure Assessment Survey. *J Exposure Anal Environ Epidemiol* 1995: 5 (3): 327–358.

Phillips T.M. Assessing environmental exposure in children: immunotoxicology screening. *J Exposure Anal Environ Epidemiol* 2000 (this issue).

Pirkle J.L., Needham L.L., and Sexton K. Improving exposure assessment by monitoring human tissues for toxic chemicals as part of a National

Human Exposure Assessment Survey. *J Exposure Anal Environ Epidemiol* 1995: 5: 403–422.

Poirier M.C., Santella R.M., and Weston A. Carcinogen macromolecular adducts and their measurement. *Carcinogenesis* 2000: 21: 353–359.

Quackenboss J.J., Pellizzari E.D., Shubat P., Whitmore R.W., Adgate J.L., Thomas K.W., Freeman N.C.G., Stroebel C., Lioy P.J., Clayton C.A., and Sexton K. Design strategy for assessing multi-pathway exposure for children: the Minnesota children's pesticide exposure study (MNCPES). *J Exposure Anal Environ Epidemiol* 2000: 10 (2): 145–158.

Raymer J.H., Pellizzari E.D., Childs B., Briggs K., and Shoemaker J.A. Analytical methods for water disinfection by-products in foods and beverages. *J Exposure Anal Environ Epidemiol* 2000 (this issue).

Rogan W.J. Environmental poisoning of children — lessons from the past. *Environ Health Perspect* 1995: 103 (6): 19–23.

Rylander R., and Etzel R. Indoor mold and children's health. *Environ Health Perspect* 1999: 107 (suppl 3): 463–517.

Schneider D., and Freeman N.C.G. Childhood environmental health risks: a state-of-the-art conference. *Archives Environ Health* 2000 (in press).

Sexton K. (Ed.). Special Issue: National Human Exposure Assessment Survey (NHEXAS). *J Exposure Anal Environ Epidemiol* 1995: 5 (3): 229–444.

Sexton K., Selevan S.G., Wagener D.K., and Lybarger J.A. Estimating human exposures to environmental pollutants: Availability and utility of existing databases. *Arch Environ Health* 1992: 47 (6): 398–407.

Sexton K., Callahan M.A., and Byran E.F. Estimating exposure and dose to characterize health risks: the role of human tissue monitoring in exposure assessment. *Environ Health Perspect* 1995: 103 (suppl 3): 13–29.

Sexton K., Greaves I.A., Church T.R., Adgate J.L., Ramachandran G., Tweedie R.L., Fredrickson A., Geisser M., Sikorski M., Fischer G., Jones D., and Ellringer P. A school-based strategy to assess children's environmental exposures and related health effects in economically disadvantaged urban neighborhoods. *J Exposure Anal Environ Epidemiol* 2000 (this issue).

Shealy D.B., Bonin M.A., Wooten J.V., Ashley D.L., Needham L.L., and Bond A. Application of an improved method for the analysis of pesticides and their metabolites in the urine of farmer applicators and their families. *Environ Int* 1996: 22 (6): 661–675.

Shuker D.E.G., and Farmer P.B. Relevance of urinary DNA adducts as markers of carcinogen exposure. *Chem Res Toxicol* 1992: 5: 450–460.

Stoeppler M., and Brandt K. Determination of cadmium in whole blood and urine by electrothermal atomic-absorption spectrophotometry. *Fresenius' Z Anal Chem* 1980: 300: 372–380.

Ting B.G., Paschal D.C., and Caldwell K.L. Determination of thorium and uranium in urine with inductively coupled argon plasma mass spectrometry. *J Anal At Spectrom* 1996: 11: 339–342.

U.S. Environmental Protection Agency (EPA). Protein Adduct Forming Chemicals for Exposure Monitoring: Chemicals Selected for Further Study. EPA/600/4-89/035, Washington, DC, 1989.

U.S. Environmental Protection Agency (EPA). Exposure Factors Handbook, Washington, DC, 1997.

U.S. Environmental Protection Agency. Strategy for Research on Environmental Risks to Children. External Peer Review Draft, Washington, DC, August 3, 1999a.

U.S. Environmental Protection Agency (EPA). Sociodemographic Data used for Identifying Potentially Highly Exposed Populations. EPA/600/R-99/060, Washington, DC, 1999b.

Valentin-Blasini L., Blount B.C., Rogers H.S., and Needham L.L. HPLC-MS/MS for the measurement of seven phytoestrogens in human serum and urine. *J Exposure Anal Environ Epidemiol* 2000 (this issue).

Wargo J. Our Children's Toxic Legacy. 2nd edn. Yale University Press, New Haven, CT, 1998.

Whyatt R.M., and Perera F.P. Application of biologic markers to studies of environmental risks in children and developing fetus. *Environ Health Perspect* 1995: 103 (suppl 6): 105–110.